

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>6</sup> :</b> <b>C07D 333/20, A61K 31/38</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/33880</b> <b>(43) International Publication Date:</b> 18 September 1997 (18.09.97)
<b>(21) International Application Number:</b> PCT/US97/03410 <b>(22) International Filing Date:</b> 7 March 1997 (07.03.97)  <b>(30) Priority Data:</b> 60/013,157 11 March 1996 (11.03.96) US  <b>(71) Applicant (for all designated States except US):</b> ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> IYENGAR, Smriti [IN/US]; 1507 Redwood Drive, Carmel, IN 46032 (US). MUHLHAUSER, Mark, A. [US/US]; 3308 Loftus Court, Indianapolis, IN 46268 (US). THOR, Karl, B. [US/US]; 109 Draymore Way, Morrisville, NC 27560 (US).  <b>(74) Agents:</b> GAYLO, Paul, J. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHODS OF TREATING OR PREVENTING INTERSTITIAL CYSTITIS		
<b>(57) Abstract</b>  This invention provides methods for the treatment or prevention of interstitial cystitis or urethral syndrome in a mammal which comprise administering to a mammal in need thereof an effective amount of duloxetine.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

- 1 -

Title**METHODS OF TREATING OR PREVENTING  
INTERSTITIAL CYSTITIS**

5

**Background of the Invention**

Interstitial cystitis is a chronic debilitating inflammatory disorder of the bladder. The disease is most common in women ranging in age from about thirty to sixty with onset of the condition typically occurring at about forty years of age. It is characterized by a number of urinary difficulties, such as suprapubic pressure and pain, with bladder filling, urinary frequency, nocturia, dysuria, urgency and irritative voiding associated with morphological and histological changes in the bladder. The condition is characterized as "interstitial cystitis" because it is believed the condition does not affect the surface of the bladder, but instead involves the spaces between the cells, namely the interstices, in the lining of the bladder.

Urethral syndrome is a related painful voiding disorder of unknown etiology affecting women exhibiting many of the conditions set forth above.

As noted in United States Patent 5,145,859, issued September 8, 1992, the entire contents of which are herein incorporated by reference, there are a number of compounds proposed to treat these conditions, based on differing theories as to the etiology of interstitial cystitis and urethral syndrome. None of these treatment regimens has proven completely successful to date.

Because of the current dissatisfaction of the currently marketed treatments for interstitial cystitis within the affected population, there exists a need for a more efficacious and safe treatment.

**Summary of the Invention**

This invention provides methods for the treatment or prevention of interstitial cystitis or urethral syndrome in a mammal

- 2 -

which comprise administering to a mammal in need thereof an effective amount of duloxetine.

### Detailed Description and Preferred Embodiments

5 Duloxetine is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine. It is usually administered as the (+) enantiomer, and as the hydrochloride salt. It was first taught by U.S. Patent 4,956,388, which teaches the synthesis of the compound as well as its high  
10 potency as an uptake inhibitor of both serotonin and norepinephrine. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule, as well as to either an enantiomer or the racemate. It is to be understood, however, that the (+) enantiomer is preferred.

15 The term "treating" (or "treat") as used herein includes its generally accepted meaning which encompasses prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or a resultant symptom. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

20 Duloxetine is a safe drug, and its use in treating or preventing interstitial cystitis or urethral syndrome, in both adults and children, is a superior treatment for that disorder because of its improved safety. The compound is particularly selective, having few if any physiological effects besides those on norepinephrine and serotonin  
25 processing, and therefore is free of side effects and unwanted activities. Further, it is effective at relatively low doses, as discussed below, and may safely and effectively be administered once per day. Thus, difficulties created by the multiple dosing of patients, who are children and disorganized adults, are completely avoided.

30 The most preferred dose of duloxetine for the treatment of a given patient with any particular disorder will vary, depending on the characteristics of the patient, as all clinicians and medical doctors are aware. Factors such as other diseases from which the patient suffers, the patient's age and size, and other medications which the patient may be  
35 using will have an effect on the duloxetine dose and will be taken into

- 3 -

account. In general, however, the daily dose of duloxetine is from about 1 to about 80 mg. A more preferred dose range is from about 5 to about 40 mg, and another preferred range is from about 5 to about 20 mg, administered once daily.

5 Duloxetine is orally available and presently is orally administered, in the form of a tablet or a capsule full of enteric coated granules. Oral administration in such forms is preferred in the practice of the present invention. However, other routes of administration are also practical and may be preferred in certain cases. For example,  
10 transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. Sustained release formulations, oral or percutaneous, may be prepared, but are not preferred because duloxetine is quite effective when administered once daily and there is little benefit from the additional effort of preparing the  
15 sustained action product.

In general, the formulation of duloxetine for use in the present invention follows the methods used in formulating duloxetine for other purposes, and indeed methods usual in pharmaceutical science are appropriate. However, a preferred formulation of duloxetine comprises  
20 enteric pellets, or granules, of which a number are charged in a gelatin capsule.

The preferred duloxetine enteric formulation comprises a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising  
25 hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such formulation.

#### Example

30 10 mg Duloxetine base/capsule

#### Bill of Materials

##### Beads

Sucrose - starch nonpareils,

20-25 mesh

60.28 mg

35

- 4 -

	<b>Duloxetine layer</b>	
	Duloxetine	11.21
	Hydroxypropylmethylcellulose	3.74
5	<b>Separating layer</b>	
	Hydroxypropylmethylcellulose	2.51
	Sucrose	5.00
	Talc, 500 mesh	10.03
10	<b>Enteric layer</b>	
	HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05
	Triethyl citrate	5.00
	Talc, 500 mesh	7.52
15	<b>Finishing layer</b>	
	Hydroxypropylmethylcellulose	8.44
	Titanium dioxide	2.81
	Talc	Trace
20		141.60 mg

The duloxetine layer was built up by suspending duloxetine in a 4% w/w solution of the hydroxypropylmethyl-cellulose in water, and milling the suspension with a CoBall Mill (Fryma Mashinen AG, Rheinfelden, Switzerland) model MS-12. A fluid bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The separating layer was added from a 4% w/w solution of the hydroxypropyl-methylcellulose in water, in which the sucrose was also dissolved.

In order to prepare the enteric coating suspension, purified water was cooled to 10°C and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the HPMCAS and talc were added and agitated until homogeneity was obtained, and the HPMCAS was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The enteric suspension was maintained at 20°C

- 5 -

during the coating process. The enteric suspension was then added to the partially completed pellets in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50°C. The product was dried in the Wurster at 50°C when the enteric suspension  
5 had been fully added, and then dried on trays for 3 hours in a dry house at 60°C. A finishing layer was then applied which consisted of a 4.5% w/w/ hydroxypropylmethyl-cellulose solution containing titanium dioxide and propylene glycol as plasticizer. The pellets were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

10 The patient to be benefited by practice of the present invention is a patient having one or more of the disorders discussed in detail below, or who is at a heightened risk of contracting such disorder. Diagnosis of these disorders, or the identification of a patient at risk of one or more of them, is to be made by a physician or psychiatrist. It is presently believed  
15 that duloxetine's potency in inhibiting the uptake of serotonin and norepinephrine is the mechanism by which it benefits such patients, by alleviating the effects of the disorder from which the patient suffers, or even eliminating the disorder completely.

20 It has been determined that the method of the present invention is effective in treating mammals, particularly middle-aged women, exhibiting symptoms of interstitial cystitis and/or urethral syndrome. In this regard, the clinical and local immune response to the compounds of the present invention is investigated in an open trail with  
25 10 female interstitial cystitis patients, whose disease is diagnosed according to the consensus criteria developed in 1987 at a National Institutes of Health workshop. To make objective the symptoms and the clinical response of the patients the present inventors scored (scale 0 to 2) the symptoms of frequency, urgency, nocturia, dysuria and suprapubic  
30 pain, as described in United States Patent 5,145,859, issued September 8, 1992, the entire contents of which are herein incorporated by reference. A compound of the present invention is administered as a single daily dose determined by a dose-titration test. Urinary interleukin-2 inhibitory activity (IL-2-IN), a marker of cell-mediated inflammation, is measured  
35 using a murine interleukin-2 dependent cell line.

- 6 -

The patients are reviewed for reduction in clinical symptoms. Drug side-effects are minimal. Urinary IL-2-IN activity before therapy confirms the presence of cell-mediated inflammation: after 4 months of therapy IL-2-IN activity is normal in most of the patients; regardless of the severity of symptoms, which indicates that the compounds of Formula I exerts an immunosuppressive effect. The data suggests that the compounds of Formula I can be an efficacious, well-tolerated, convenient oral medication for the treatment of interstitial cystitis.

In addition, as more clearly demonstrated below in Example 2, the present inventors also observes similar responses in regard to the treatment of urethral syndrome. As a result, the test data clearly indicates that the compounds employed in the present invention can be effective therapeutic agents for the treatment of interstitial cystitis and/or urethral syndrome.

As a result, it has been found that duloxetine is particularly well-suited for the treatment of interstitial cystitis and/or urethral syndrome because they not only provide effective relief, are available for oral administration, and are relatively inexpensive. It has been discovered that patients receiving duloxetine substantially reduce the pathological conditions exhibited by these two painful bladder disorders, and are able to carry on their daily activities in a relatively normal existence in comparison with their pre-treatment state.

The present invention will be further described according to the following non-limiting examples.

### Example 1

#### Materials and Methods

**Patients.** The diagnosis of interstitial cystitis is assigned to 10 female patients, aged 23 to 51 years, in accordance with the consensus criteria established at the National Institutes of Health workshop on interstitial cystitis, August, 1987 (Gillenwater, J. Y. and Wein, A. J.: Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda,



- 7 -

Md., Aug. 28-29, 1987, J. Urol., 140:203, 1988), and United States Patent 5,145,859:

**Interstitial Cystitis: Criteria for Diagnosis**

5

<b><u>Inclusion Criteria</u></b>	<b><u>Exclusion Criteria</u></b>
Hunner's Ulcer (if present, automatic inclusion)	less than 18 years old benign or malignant tumors radiation, tuberculous, bacterial
Positive Factors (at least 2 required for inclusion):	or cyclophosphamide cystitis vaginitis
suprapubic, pelvic, urethral, vaginal or perineal pain	duration of symptoms < 1 year gynecologic cancer urethral diverticulum, bladder or lower ureteral calculi
glomerulations at cystoscopy after bladder distension (80 cm water pressure x 1 min.)	active herpes (HSV II) waking frequency < 5 in 12 hrs. nocturia < 2
decreased compliance on cystometrogram	neurogenic bladder dysfunction waking capacity > 400 ml, absence of urgency with bladder filling
pain on bladder filling relieved by emptying	symptoms relieved by antibiotics, urinary urinary analgesics or antiseptics

Cystometrics are performed after cessation of other modes of therapy and prior to institution of therapy: all patients had a waking bladder capacity of less than 350 ml (range 150 ml to 340 ml).

10

- 8 -

**Symptom Evaluation:** The symptom scores (total score range: 0 to 10) form the basis for the evaluation of treatment efficacy. The severity of each symptom is assigned a numerical value, as follows:

5

**Symptom Severity Survey**

Symptom	Description	Score
Frequency (daytime)	voids once every 3 to 5 hours	0
	voids once every 1 to 2 hours	1
	voids more than once every hour	2
Urgency	urge to void equal to actual frequency	0
	urge to void exceeds actual frequency	1
	constant urge to void	2
Nocturia	no nocturia, or 1 void nightly	0
	nocturia 2 to 4 times nightly	1
	more than 4 times nightly	2
Dysuria	no dysuria	0
	intermittent dysuria	1
	dysuria with each void	2
Suprapubic pain (abdomino- perineal)	no pain	0
	intermittent pain	1
	constant pain	2

At the time of diagnosis, and before any treatment, any patient who falls within the parameters of the inclusion or exclusion descriptors of the NIH workshop consensus criteria (above) will score at least a "4" on this survey (frequency < 1; urgency < 1; nocturia < 1; and either dysuria or suprapubic pain < 1).

**Urine Collection:** Urine specimens are collected from all patients before and during therapy. Voided urine is centrifuged at 1000 x g for 10 minutes at 4°C and the supernatant separated from the sediment. The urine supernatant is subjected to 0.2 µ filtration (celluloseacetate) at

- 9 -

4°C to remove any bacteria and debris, and a 1 ml aliquot is removed for creatinine measurement (CREATININE II ANALYZER™, Beckman Instruments, Inc., Brea, California). The supernatant is ultrafiltered against 3 x volume in phosphate-buffered saline (PBS) with 0.1 µg/ml albumin (Sigma, St. Louis, Missouri) using a filtration device (5,000 MW cut off; Amicon, Deavers, Massachusetts). The concentrated supernatant is dialyzed using 3,500 MW cutoff tubing, shell frozen with dry ice, and vacuum lyophilized. The powder is stored at -20°C.

10           **Measurement of IL-2-IN Activity:** The bioassay for IL-2-IN is modified from the method for measuring IL-2 activity described by Gillis and associates. S. Gillis, *et al.*, "T-Cell Growth Factor: Parameters Of Production And A Quantitative Microassay For Activity, Journal of Immunology, 120:2027, (1978). The murine IL-2-dependent cytotoxic T-  
15 cell line (CTLL-N) is derived from the CT-6 cell line. J. Kusugami, *et al.*, "Intestinal Immune Reactivity To Interleukin-2 Differs Among Crohn's Disease, Ulcerative Colitis And Controls", Gastroenterology, 97:1 (1989). The CTLL-Ns are maintained in liquid culture using a 1:1 mixture of Roswell Park Memorial Institute (RPMI) 1640 and Dulbecco's Modified  
20 Eagles Medium (DMEM; 4.5 g/L glucose) media supplemented with 2.9 mg/ml glucose, 9.4 mM HEPES buffer, 1.9 mg/ml glutamine, 289 µg/ml arginine, 0.12 M non-essential amino acids,  $5 \times 10^{-5}$  M 2-mercaptoethanol, 4.5% fetal bovine serum, 90 units/ml penicillin, 90 µg/ml streptomycin, 22 µg/ml fungizone, 0.45 mg/ml gentamicin and 20 units/ml of human  
25 recombinant IL-2.

          The CTLL-Ns are washed and suspended at a concentration of  $10^5$ /ml in the culture media. Assays are performed in triplicate, as follows: a serial dilution of the sample aliquot (50 µl), a 1:10 dilution of the human recombinant IL-2 standard and  $10^4$  CTLL-Ns (100 µl) are  
30 placed in microliter wells. The microliter plates are incubated in a humidified 6% CO<sub>2</sub> atmosphere at 37°C. for 24 hrs, and the cells are pulsed at the 19th hour with 1 µCi/well of methyl-tritiated thymidine (specific activity 6.7 Ci/mM, New England Nuclear, I. E. Dupont, Boston, Massachusetts).

- 10 -

The cells are collected onto glass filter paper discs. The discs are placed in scintillation fluid and thymidine uptake is measured by liquid scintillation spectrophotometry. IL-2 inhibitory activity is calculated by modified probit analysis.

5           The proliferation "maximum" is the tritiated thymidine uptake caused by the amount of exogenous IL-2 activity in the control microliter wells, assessed in quadruplicate for each assay. The proliferation "minimum" is derived from lowest amount of tritiated thymidine uptake caused by the IL-2 inhibitor standard. The probit  
10 calculation corrected for minor interassay variations of thymidine uptake in control wells, and permitted interassay comparisons of inhibitor activity among the urine samples. By this treatment of the data, the calculated value of IL-2 inhibitory activity in lyophilized urine samples varies less than 10% from assay to assay. IL-2-IN activity is expressed in  
15 units/mg urine creatinine (U/mg u.c.). IL-2-IN activity is less than 0.05 U/mg u.c. in the urine of healthy adults. J. Fleischmann, et al., Journal of Biological Regulators and Homeostatic Agents, 4:73, (1990).

20           Medication Assignments: All patients are treated initially with a total daily dose of 30 mg, which is administered as a single, extended release tablet.

25           Patient Monitoring: Patients are interviewed and blood pressure measured twice monthly during the first 2 months of therapy, during the first 2 months after a dose escalation, and then once monthly thereafter. The symptom severity score at each interview is based on the patient's experiences during the previous 24 hours.

### Example 2

30           In addition to the treatment of patients with interstitial cystitis, patients with the urethral syndrome have been treated with duloxetine, using the titration test and treatment protocol described in United States Patent 5,145,859. Similar to the data of Example 1, the  
35 positive response to the compounds of the present invention in this limited

- 11 -

study supports the hypothesis that the urethral syndrome and interstitial cystitis are both part of the same disease spectrum, perhaps as variants of reflex sympathetic dystrophy.

5           The invention has been described with reference to the preferred embodiment. Obviously, modifications and alterations will occur to others upon a reading and understanding of this specification. It is intended to include all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents  
10 thereof.

          While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical  
15 compositions comprising a pharmaceutically acceptable excipient and at least one active ingredient. These compositions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Many of the compounds employed in the methods of this invention are effective as both injectable  
20 and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

          In making the compositions employed in the present  
25 invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the  
30 compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile  
35 packaged powders.

- 12 -

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual

- 13 -

compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower  
5 limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day. In addition to the enteric tablet formulation described, supra, the present invention also  
10 employs methods of treating or preventing interstitial cystitis or urethral syndrome employing duloxetine in a number of formulations. Examples of such formulations follow.

#### Formulation Preparation 1

15

Hard gelatin capsules containing the following ingredients are prepared:

20	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient(s)	30.0
	Starch	305.0
25	Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

- 14 -

**Formulation Preparation 2**

A tablet formula is prepared using the ingredients below:

5		Quantity
	<b><u>Ingredient</u></b>	<b><u>(mg/tablet)</u></b>
	Active Ingredient(s)	25.0
	Cellulose, microcrystalline	200.0
10	Colloidal silicon dioxide	10.0
	Stearic acid 5.0	

15                   The components are blended and compressed to form tablets,  
each weighing 240 mg.

**Formulation Preparation 3**

20                   A dry powder inhaler formulation is prepared containing the  
following components:

	<b><u>Ingredient</u></b>	<b><u>Weight %</u></b>
	Active Ingredient(s)	5
25	Lactose	95

The active mixture is mixed with the lactose and the mixture  
is added to a dry powder inhaling appliance.

30



- 15 -

**Formulation Preparation 4**

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

5		Quantity
	<b><u>Ingredient</u></b>	<b><u>(mg/tablet)</u></b>
	Active Ingredient(s)	30.0 mg
10	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone	
15	(as 10% solution in water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
20	Talc	<u>1.0 mg</u>
	Total	120 mg

25           The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium

30 carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

- 16 -

**Formulation Preparation 5**

Capsules, each containing 40 mg of medicament are made as follows:

5

<b><u>Ingredient</u></b>	<b><u>Quantity</u></b>
<b>Active Ingredient(s)</b>	<b>(mg/capsule)</b>
	40.0 mg
10 Starch	109.0 mg
Magnesium stearate	<u>1.0 mg</u>
Total	150.0 mg

15

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

20

**Formulation Preparation 6**

Suppositories, each containing 25 mg of active ingredient are made as follows:

25

<b><u>Ingredient</u></b>	<b><u>Amount</u></b>
<b>Active Ingredient(s)</b>	<b>25 mg</b>
Saturated fatty acid glycerides to	2,000 mg

30

The active ingredient(s) is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

- 17 -

**Formulation Preparation 7**

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

5	<b><u>Ingredient</u></b>	<b><u>Amount</u></b>
	Active Ingredient(s)	50.0 mg
	Xanthan gum	4.0 mg
10	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.0 mg
	Sucrose	1.75 g
15	Sodium benzoate	10.0 mg
	Flavor and Color	q.v.
20	Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

- 18 -

**Formulation Preparation 8**

Capsules, each containing 15 mg of medicament, are made as follows:

5

<b><u>Ingredient</u></b>	<b><u>Quantity</u></b>
<b>Active Ingredient(s)</b>	<b>15.0 mg</b>
<b>Starch</b>	<b>407.0 mg</b>
<b>Magnesium stearate</b>	<b><u>3.0 mg</u></b>
<b>Total</b>	<b>425.0 mg</b>

15

The active ingredient(s), cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

20

**Formulation Preparation 9**

An intravenous formulation may be prepared as follows:

25

<b><u>Ingredient</u></b>	<b><u>Quantity</u></b>
<b>Active Ingredient(s)</b>	<b>250.0 mg</b>
<b>Isotonic saline</b>	<b>1000 ml</b>

30

- 19 -

**Formulation Preparation 10**

A topical formulation may be prepared as follows:

5	<b><u>Ingredient</u></b>	<b><u>Quantity</u></b>
	Active Ingredient(s)	1-10 g
	Emulsifying Wax	30 g
10	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

- 15 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

- 20 -

**Formulation Preparation 11**

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

5

<b><u>Ingredient</u></b>		<b>Quantity</b>
<b>Active Ingredient(s)</b>		<b><u>Per Tablet</u></b>
		<b>10.0 mg</b>
10	<b>Glycerol</b>	<b>210.5 mg</b>
	<b>Water</b>	<b>143.0 mg</b>
	<b>Sodium Citrate</b>	<b>4.5 mg</b>
15	<b>Polyvinyl Alcohol</b>	<b>26.5 mg</b>
	<b>Polyvinylpyrrolidone</b>	<b><u>15.5 mg</u></b>
	<b>Total</b>	<b>410.0 mg</b>

20

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

30

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g.,

35

- 21 -

U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

5 Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S.  
10 Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs.  
15 Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can  
20 transiently open the blood-brain barrier.

- 22 -

We Claim:

1. A method for the treatment or prevention of interstitial  
cystitis or urethral syndrome in a mammal which comprise administering  
5 to a mammal in need thereof an effective amount of duloxetine.

2. A method as claimed in Claim 1 wherein the mammal  
is administered between 30 and 150 mg of duloxetine per day.

10 3. A method as claimed in Claim 2 wherein the  
duloxetine is administered as an enteric tablet.

4. Duloxetine for use in treating or preventing interstitial  
cystitis or urethral syndrome.

15

5. A pharmaceutical formulation containing, as an active  
ingredient, duloxetine adapted for use in the treatment or prevention of  
interstitial cystitis or urethral syndrome.

20 6. The use of duloxetine for the manufacture of a  
medicament for the treatment or prevention of interstitial cystitis or  
urethral syndrome.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/03410

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 333/20; A61K 31/38

US CL :549/75; 514/438

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/75; 514/438

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Medline

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOR et al. Effects of Duloxetine, a Combined Serotonin and Norepinephrine Reuptake Inhibitor, on Central Neural Control of Lower Urinary Tract Function in the Chloralose-Anesthetized Female Cat. The Journal of Pharmacology and Experimental Therapeutics. 1995, Vol. 274, No. 2, pages 1014-1024, see entire document.	1-6

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
* A	document defining the general state of the art which is not considered to be of particular relevance		
* E	earlier document published on or after the international filing date	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* O	document referring to an oral disclosure, use, exhibition or other means		
* P	document published prior to the international filing date but later than the priority date claimed	* A	document member of the same patent family

Date of the actual completion of the international search

05 JUNE 1997

Date of mailing of the international search report

11 JUL 1997

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ROBERT GERSTL aco

Telephone No. (703) 308-1235



## DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPERATION EN MATIÈRE DE BREVETS (PCT)

<b>(51) Classification internationale des brevets <sup>6</sup> :</b> <b>A61K 31/13, 9/50</b>	<b>A1</b>	<b>(11) Numéro de publication internationale:</b> <b>WO 98/08495</b> <b>(43) Date de publication internationale:</b> 5 mars 1998 (05.03.98)
<b>(21) Numéro de la demande internationale:</b> PCT/FR97/01525 <b>(22) Date de dépôt international:</b> 26 août 1997 (26.08.97) <b>(30) Données relatives à la priorité:</b> 96/10528 28 août 1996 (28.08.96) FR <b>(71) Déposant (pour tous les Etats désignés sauf US):</b> PIERRE FABRE MEDICAMENT [FR/FR]; 45, place Abel Gance, F-92100 Boulogne-Billancourt (FR). <b>(72) Inventeurs; et</b> <b>(75) Inventeurs/Déposants (US seulement):</b> PAILLARD, Bruno [FR/FR]; 5, impasse Gaugin, F-63540 Romagnat (FR). GOUTAY, Eric [FR/FR]; 36, les Côteaux de Marrast, F- 31650 Lauzerville (FR). AVAN, Jean-Louis [FR/FR]; Les 4 Moulins, 24, avenue de Verdun, F-31290 Villefranche de Lauragais (FR). BOUGARET, Joël [FR/FR]; Rue de la Mairie, F-31570 Lanta (FR). <b>(74) Mandataires:</b> MARTIN, Jean-Jacques etc.; Cabinet Regim- beau, 26, avenue Kléber, F-75116 Paris (FR).		<b>(81) Etats désignés:</b> AU, BR, CA, CN, JP, KR, MX, NZ, US, brevet européen (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Publiée</b> <i>Avec rapport de recherche internationale.</i> <i>Avant l'expiration du délai prévu pour la modification des</i> <i>revendications, sera republiée si de telles modifications sont</i> <i>reques.</i>
<b>(54) Title:</b> GALENIC FORMULA WITH EXTENDED RELEASE OF MILNACIPRAN <b>(54) Titre:</b> FORME GALENIQUE A LIBERATION PROLONGEE DE MILNACIPRAN <b>(57) Abstract</b> <p>The invention concerns a galenic formula with prolonged release, for oral administration of a single daily dose of 60 to 140 mg of Milnacipran, having a multi-particulate form containing a plurality of microgranules each comprising an active microsphere containing a saccharose and/or starch nucleus of a size grade between 200 and 2000 <math>\mu</math>m and containing 150 to 1000 <math>\mu</math>m of Milnacipran and a binding agent, each microgranule being coated with a film, with a base of at least one polymer insoluble in water but permeable to physiological liquids, of a thickness between 20 and 100 <math>\mu</math>m, the said galenic formula enabling an in vitro release corresponding to the following pattern: between 10 and 55 % of the dose released in 2 hours, between 40 and 75 % of the dose released in 4 hours, between 70 and 90 % of the dose released in 8 hours, between 80 and 100 % of the dose released in 12 hours.</p> <b>(57) Abrégé</b> <p>L'objet de la présente invention concerne une forme galénique à libération prolongée, destinée à l'administration par voie orale en une prise journalière unique de 60 à 140 mg de Milnacipran, se présentant sous une forme multiparticulaire réunissant une pluralité de minigranules comportant chacune une minisphère active comprenant un noyau de saccharose et/ou d'amidon de granulométrie comprise entre 200 et 2000 <math>\mu</math>m et renfermant de 150 à 1000 <math>\mu</math>g de Milnacipran ainsi qu'un agent liant, chaque minigranule étant enrobée par un film, à base d'au moins un polymère non hydrosoluble mais perméable aux liquides physiologiques, d'épaisseur comprise entre 20 et 100 <math>\mu</math>m, ladite forme galénique permettant une libération in vitro correspondant au profil suivant: entre 10 et 55 % de la dose libérée en 2 heures; entre 40 et 75 % de la dose libérée en 4 heures; entre 70 et 90 % de la dose libérée en 8 heures; entre 80 et 100 % de la dose libérée en 12 heures.</p>		